How to treat patients with relapsed/refractory multiple myeloma: evidence-based information and opinions

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Abstract

Relapsed/refractory multiple myeloma (rrMM) remains a difficult condition to treat, despite the availability of new drugs. In this review, we searched for evidence to guide physician in the choice of salvage therapy in certain subgroups of patients. We tried to provide evidence-based information and to suggest possible approaches based on data on prior therapies, prior remission duration, toxicity of prior treatments, patient's comorbidities and disease characteristics at relapse. Unfortunately, little evidence is available, there are no large and/or randomized trials nor direct comparisons of drugs or combinations for rrMM patients to draw any definite conclusion. Almost all the studies presented here suggest that depth of response is a key factor also for patients with rrMM. Which one between combinations and sequential therapies is the best approach remains controversial. Several studies favor the former approach in early relapse, since it leads to a higher complete response rate, regardless of prior therapies. However, in both strategies, achieving maximal response should always remain a main goal. Consolidation/maintenance therapy is beneficial both in combination or sequential therapies also in rrMM. Second generation new-drugs, such as pomalidomide, carfilzomib, bendamustine and histone-deacetylase inhibitors, will probably expand the rescue possibilities also in this setting.

Introduction

Novel agents, namely the immunomodulatory drugs Thalidomide and Lenalidomide, and the proteasome inhibitor Bortezomib, were tested in different clinical trials and led to good results in patients with multiple myeloma (MM). In particular, benefits with novel agents were also seen in relapsed/refractory multiple myeloma (rrMM)[1].

Besides the approved regimens, new combinations containing novel drugs with/without conventional chemotherapies and/or steroids have been studied for the treatment of rrMM. To date, no comparative studies are available to help physicians choose the best treatment for rrMM patients. Treatment choice for rrMM is based on prior therapy, remission duration and toxicity of treatment, patient's comorbidities and disease characteristics at relapse. Direct evidence and more precise guidelines are needed.

This review reports on the latest data and evidence about treatment of rrMM.

Is quality of response a critical end-point?

In newly diagnosed multiple myeloma (MM) patients, a complete response (CR) is a surrogate marker of long-term outcome. After the introduction of novel drugs, CR has become a more achievable aim, also for rrMM patients. However, the role of CR in these patients needs to be validated. Table 1 summarizes the studies addressing this issue. A retrospective study investigated the relationship between response rate and outcome in more than 300 patients with rrMM treated

with thalidomide ± dexamethasone. In this study, the achievement of CR and very good partial response (VGPR) was associated with a significantly longer progression-free survival (PFS) and overall survival (OS) compared with partial response (PR) and stable disease (SD)[2]. In another retrospective analysis on rrMM patients treated with the combination of Doxil, Vincristine, low-dose dexamethasone and Thalidomide (DVd-T) found that patients achieving CR/VGPR had a significantly better PFS and OS compared with those achieving PR/SD[3].

In the randomized phase III APEX trial, a post-hoc analysis including patients treated with bortezomib as single agent showed a relation between CR and both better treatment free interval (TFI) and better time to alternative therapy (TTAT), although time-to-progression (TTP) and OS were similar[4]. These results were consistent with those reported in a retrospective analysis on 70 patients treated with bortezomib ± dexamethasone[5]. Patients obtaining CR/VGPR had a considerably better TTP, TTAT, TFI compared with those achieving PR. In another study, the combination of bortezomib with doxorubicin and dexamethasone led to a significant higher event-free survival (EFS) in patients obtaining CR/VGPR if compared with PR[6]. In a recent observational study, 769 patients were treated with bortezomib-based therapy. After at least 4 courses of therapy, CR rate was 12% and near CR (nCR) 16%[7]. These patients had a significantly improved survival compared with those who did not achieved CR and nCR. Another trial assessed the role of the 4-drug combination Thalidomide-Doxil-Dexamethasone-Bortezomib (ThaDD-V)[8]. Patients who achieved CR had a significantly longer PFS compared with those achieving a lower response. In this study, patients attaining a stringent CR (sCR) had a better outcome than those achieving CR only. This demonstrates the importance of a deeper response also in rrMM.

A post-hoc analysis pooled data from two trials comparing patients treated with lenalidomide and high-dose dexamethasone[9]. In this analysis, patients achieving CR/VGPR had a significantly better TTP and OS compared with those achieving PR. This benefit was independent of when CR/VGPR was achieved and it was confirmed by a landmark analysis at 12-months. However, the

two groups of patients were not well balanced. Patients who achieved CR/VGPR had a shorter disease history and received less prior treatments, particularly with thalidomide. No adjustment for these important factors was made in this study, and this is a major limitation.

These studies suggest that rrMM patients who achieve deeper response have a better outcome, at least in terms of PFS. These data should be considered with caution, since they derive from retrospective studies. Well-designed prospective studies are warranted to establish the relationship between response and outcome in rrMM.

Choosing treatment for patients with suboptimal response to induction regimen

Overall response rate (ORR/ at least PR) after first-line therapy with novel agents accounts for 57-100%[10-12]. MM patients considered "truly" refractory to induction therapy,i.e. those who fail to reach at least PR after three cycles of induction with novel agent-containing therapy, as defined in recent guidelines provided by an international panel of experts [13], may need salvage treatment

In the non-transplant setting, the role of therapy aiming to improve depth of response should be investigated. No benefit with this approach was seen in elderly patients failing to reach at least PR, since these patients may have difficulties in prolonging treatment. Better quality of response was associated with improved long-term outcomes with VMP treatment, regardless of whether best response, in particular CR, was achieved early or late (even after 24 weeks of treatment). This was particularly evident in older patients and in those with high serum β2-microglobulin levels or higher tumor burden (ISS stage II or III)[14]. Prolonging lenalidomide-based treatment was linked to an improvement in quality of response[15]. These data suggest that initial treatment should be continued beyond first response, if tolerated, in order to achieve higher quality response. Ongoing or future prospective trials addressing this issue will validate this approach. This should be always considered an individualized approach and should be based on patient's characteristics such as age, performance status, presence of comorbidities, type of previous therapy, quality of response achieved, tolerance to therapy, side-effects of drugs. Some important aspects should be considered,

such as risk of disease, possible worsening of quality of life due to prolonged treatment, poor outcome after relapse/refractory to novel agents, and drug resistance at relapse. These factors may reduce the spectrum of new therapeutic options that can be used. However, stabilization of a symptom-free condition despite evidence of persistent disease should remain a major goal in unfit elderly patients, while, in the other patients, treatment should aim at achievement of the best possible response.

In the transplant setting, not achieving at least PR after induction therapy with old agents did not affect PFS or OS, and a response was achieved after transplantation [16,17]. However, different outcomes were reported according to the depth of response achieved. Conversely, a recent retrospective analysis of 286 patients showed that failure to respond to immunomodulatory-based (IMiD, thalidomide or lenalidomide) induction treatment leads to significantly shorter post-transplant PFS and OS[18]. This study also suggested that the mechanisms underlying resistance to IMiD therapies are similar to those with high-dose melphalan. This observation raises the question of whether patients not responding to induction regimens including novel agents should be immediately treated with alternative therapies before transplant.

So far, induction therapy has aimed to achieve the deepest and fastest response before transplantation. No data are currently available on possible consolidation after induction and before transplantation for patients achieving "suboptimal" response to induction. New studies are ongoing to further improve the results obtained after induction treatments, by reducing doses (thus increasing tolerability), adding a fourth drug to the regimen used, or combining the two most potent agents (bortezomib and lenalidomide)[19-21]. Besides risk-adapted therapies, in the near future, response-adapted strategies may have a fundamental role to choose treatment and to further improve outcome.

How many drugs in rrMM?

Three- and 4-drug combinations improve CR rate and outcome of newly diagnosed MM[22]. Is it the same also for rrMM?

The CR rate with approved single- or 2-agent therapies for rrMM such as bortezomib[23] lenalidomide[24], bortezomib-doxil[25] and lenalidomide-dexamethasone[26,27] ranges from 2 to 15%, TTP from 5 to 11 months. Many 3- or 4-drug combinations have been recently studied in phase I-II studies in patients with rrMM. CR rates and PFS of the main regimens used in rrMM are reported in the Fig. 1. Data show that a more intense approach leads to higher CR rate and subsequently to better outcome. Three- or 4-drug combinations containing thalidomide, bortezomib, dexamethasone and anthracyclines showed the best results in rrMM, CR rates approximately doubled and PFS improved if compared with single- or 2-agent regimens. Toxicity is not always strictly associated with the number of drugs used. As showed in Table 2, the incidence of neutropenia, infections and DVT with regimens including 3 or 4 drugs were comparable with those reported with 2-drug combinations. However, thrombocytopenia and neuropathy are more common when 3- or 4-drug combinations including bortezomib are used. In order to improve outcome by reducing toxicity, some studies demonstrated that reducing bortezomib schedule from twice- to once-weekly administration significantly decreases bortezomib-induced peripheral neuropathy [28-30]. These more complex regimens are beneficial also in rrMM, provided that patients have not particular contraindications, such as neuropathy, and if they are able to tolerate potential toxicities associated with such combinations, for instance thrombocytopenia and neuropathy. Replacing thalidomide with lenalidomide and reducing bortezomib dose-intensity may improve outcome and decrease non-hematological toxicity.

How long should rrMM therapy last?

In newly diagnosed MM, prolonged or continuous therapy (i.e. consolidation-maintenance) is associated with higher quality of response and translates into better outcome[28,31-35]. Treatment

duration is a burning question also in rrMM. Whether induction therapy should be limited to 6-9 courses and repeated if necessary, or if it should be prolonged or continued until progression remains an open issue.

Limited therapy with 3- or 4-drug combinations (i.e. lenalidomide-adriamicyn-dexamethasone [RAD] or bortezomib-melphalan-prednisone-thalidomide [VMPT])[36,37] do not improve the results obtained with 2-drug regimens such as lenalidomide-dexamethasone (LD)[38] or bortezomib-dexamethasone (VD)[39] whereas consolidation plus maintenance (i.e. bortezomib-adriamicyn-dexamethasone [PAD] followed by thalidomide-dexamethasone consolidation (TD) and thalidomide maintenance, or thalidomide-dexamethasone-doxil-bortezomib [ThaDD-V] followed by VD/TD consolidation and thalidomide maintenance)[8,40] after induction with regimens containing bortezomib triples CR rate and improves PFS.

Four-drug combinations such as dexamethasone-bortezomib-doxorubicin-lenalidomide (DVd-R)[41] or lenalidomide-melphalan-prednisone-thalidomide (RMPT)[42] followed by maintenance with lenalidomide do not seem to improve outcome compared with continuous LD.

Some studies investigated re-treatment with bortezomib after an adequate rest period. Patients enrolled in VISTA trial, who relapsed after VMP and were re-treated with bortezomib, had a CR rate similar to patients treated with lenalidomide- or thalidomide-based salvage therapy[30]. Ongoing prospective study (RETREIVE study) demonstrated that re-treatment with bortezomib is feasible and safe but the benefits of this strategy needs to be confirmed[43].

A recent sub-analysis pooled MM-09 and MM010 studies[9]. Patients achieving PR after induction with LD had 50% probability of obtaining CR/VGPR with further treatment and this response upgrade translated into a better outcome. However, in this study, 60% of patients tolerated and continued therapy after induction, and only 30% remained in the landmark analysis at 12 months. Long-term treatment with LD is feasible and well-tolerated although severe hematologic toxicity, infections and thrombosis are a considerable drawback. Further investigation will define clinical

and biological characteristics of patients who are more likely to benefit from long-term therapy. To date, no specific study has assessed which is the patient population that benefits more from this approach. In particular, the role of prolonged treatment remains controversial in elderly patients for whom long-term therapy may be detrimental. Therefore, a close evaluation of the risk/benefit ratio is warranted.

What is the impact of prior therapy?

Most young and elderly patients with newly diagnosed MM are currently treated with combinations containing at least one new drug. Identifying the best approach at relapse is difficult, especially considering that all patients have already been exposed to thalidomide, lenalidomide and bortezomib. Moreover, few data about the impact of prior therapies on quality of response and outcome in patients with rrMM are available. Before the introduction of novel agents, duration of response progressively shortened with subsequent regimens[44]. Similarly, patients who relapsed or became refractory to novel agents show a poor outcome in terms of both PFS and OS[45].

As shown in Fig. 2, in two studies, the number of previous therapy did not significantly impact on response rate in relapsed/refractory MM patients receiving either bortezomib[23] or lenalidomide monotherapy[24]. Patients included in these two studies were not matched for number of prior therapies (2 or fewer prior treatment regimens versus 3 or more in patients treated with lenalidomide; one prior line of therapy versus more than one in those receiving bortezomib). In patients heavily pre-treated, bortezomib led to a response rate similar to patients who received lenalidomide alone (at least PR 34% *vs* 26%). Considering the toxicities associated with lenalidomide/bortezomib and the possible presence of comorbidities, these agents could be used alone in elderly or frail heavily pretreated rrMM patients for whom preserving quality of life is essential.

A subset analysis of MM-009/MM-010 trials assessing LD, reported a higher ORR rate (67% *vs* 57%) and significantly longer PFS (14 months *vs* 9.5 months; p=0.047) and OS (median not

reached *vs* 30.8 months; p=0.028) in patients receiving only one prior therapy[46]. These results are consistent with those obtained in a retrospective analysis on patients receiving LD where a higher number of prior regimens was associated with lower ORR[47]. However, this trend was not confirmed in studies including patients treated with 3- or 4-drug combinations. ORR obtained in patients receiving bortezomib-lenalidomide-dexamethasone (VRD)[48] and PAD[6] was not affected by the number of prior therapies. Of note, responses with PAD as second-line treatment (at least PR=80%; CR=13.5%) were similar to PAD as fourth-line treatment (at least PR=64%; CR=12%), and no significant difference in term of 1-yr EFS was detected between patients receiving PAD as second-line or beyond[6]. On the contrary, VMPT regimen is more effective at early-stage disease, leading to a CR rate of 36% compared with 0% in patients heavily pretreated. This also translated into a significantly higher PFS (1-yr 100% *vs* 27%; p=0.009)[37]. Similar results were obtained with ThaDD-V combination[8]. No definite data are available to explain how prior therapies may impact on outcome of the 3- and 4-drug combinations described above. However, in patients who received one prior therapy, VMPT and ThaDD-V induce CR rates similar to those obtained in newly diagnosed MM. Conversely, CR rate after PAD regimen is unexpectedly low in these patients, and is comparable to results obtained with lenalidomide plus dexamethasone (Fig. 2). It is not clear if such results depend on the different study population, the limited number of patients enrolled, or any other reason. Of note, these more intense approaches are associated with grade 3-4 neutropenia, infection and peripheral neuropathy, hence they may be more suitable for younger patients or compliant patients at early relapse phase.

As for the type of previous therapies, mainly data on thalidomide and its impact on salvage therapy are available. Thalidomide was introduced before bortezomib and lenalidomide, and it has in fact been used more extensively. Data about previous therapy with thalidomide, summarized in Fig. 3 and Fig. 4, are quite conflictng Patients receiving bortezomib alone[49] showed worse response and outcome if they had received prior thalidomide; on the contrary, no differences in terms of

ORR and TTP were found in patients previously treated or not with thalidomide and receiving bortezomib plus pegylated liposomal doxorubicin[50]. Pooled data from MM-009/MM-010 trials showed that ORR and TTP were significantly lower in patients with prior thalidomide exposure, suggesting the possibility of a cross-resistance between thalidomide and lenalidomide. However, in this study, patients previously treated with thalidomide had a significant higher number of prior lines of therapy and a longer time from diagnosis[51]. These results are partly in contrast with those from a French retrospective analysis on patients treated with LD[47]. In this study, response rate and PFS were not affected by prior thalidomide, although progression on thalidomide negatively affected both PFS and OS. This may suggest the negative impact of thalidomide maintenance therapy[47,52]. Nevertheless, a recent retrospective study, including a wide cohort of heavily pretreated patients, demonstrated that lenalidomide is effective in patients both thalidomide-resistant or sensitive to a previous thalidomide-therapy.[53] Although only retrospective analyses are currently available, prior thalidomide seems to not affect salvage therapy with lenalidomide.

More complex regimens, such as the combinations bortezomib-dexamethasone-cyclophosphamide (BCD)[54], bortezomib-thalidomide-dexamethasone (VTD)[55], bortezomib-lenalidomide-dexamethasone (VRD)[48] showed a significant higher efficacy in patients who did not receive prior treatment with thalidomide or who are not resistant to it (Fig 4).

The impact of previous therapy with bortezomib is controversial. As reported in Fig. 5, two studies[26,47] with LD showed conflicting results: in one study previous bortezomib did not affect ORR, while in the other one ORR, PFS and OS were significantly better in patients who had not been previously treated with bortezomib. However, the two patient populations did not match for median number of previous regimens (2 *vs* 4, respectively). In the MM-016 study, multivariate analysis in patients treated with LD showed that prior bortezomib is an adverse risk factor affecting PFS and OS[56]. In contrast with VRD regimen[48], ORR of patients who received PAD regimen was not affected by prior bortezomib exposure, showing the efficacy of bortezomib in consecutive

lines of therapies[6]. This was also confirmed in another study using ThaDD-V combination[8]. The recent update analysis of the VISTA trial shows that bortezomib administered as first-line treatment does not negatively affect response to lenalidomide-, thalidomide- or bortezomib-based regimens at relapse[30]. Data on the impact of previous bortezomib on subsequent salvage therapies are limited and conflicting, and they mainly derive from retrospective studies including small number of patients. Therefore, no definitive conclusion can be drawn [6,8,48].

With regard to salvage treatment following LD, bortezomib-based regimens[57] in heavily pretreated patients led to at least PR rate 43% and prolonged. Another study on patients previously treated with lenalidomide, bortezomib in combination with lenalidomide and dexamethasone showed encouraging results (at least PR = 57%; CR = 15%)[58]. Lenalidomide, cyclophosphamide and prednisone (REP) may be another alternative option in this setting. In one trial, REP induced a response rate of 50% (CR = 14.3%) in patients refractory to LD[59]. On the contrary, thalidomide-based therapies do not exert a substantial activity in patients who received prior treatment with lenalidomide, although only results from very small study are available[60].

A prior stem cell transplantation does not seem affect response and outcome in patients receiving new-drug combinations[48,49,61]. In patients who relapsed after single or tandem autologous stem cell transplantation (ASCT), a recent Italian study reported a significant higher response rate in patients receiving ASCT as second-line compared with those treated with thalidomide/bortezomib based-regimens (85% *vs* 49%; p=0.0004). However, no differences in terms of PFS or OS were detected between two groups of patients [62].

What is the impact of cytogenetics in rrMM?

The prognostic value of chromosomal abnormalities such as del(13), t(4;14) or del(17p) has not been well defined in rrMM patients treated with new drugs since no prospective, randomized trials have been performed yet. In most retrospective analyses of phase II/III studies including patients

receiving single-agent or new drug combinations, del(13) by FISH was not associated with a significant lower ORR and a shorter TTP/PFS[47,56,6365]. Jagannath and colleagues evaluated the impact of del(13) identified by either FISH or methaphase cytogenetics on response and outcome in patients receiving bortezomib in SUMMIT and APEX trials. This study found no adverse prognostic impact of del(13) also by conventional cytogenetics, but the number of patients included was considerably small [64]. However, in a Korean study assessing a four-drug combination (bortezomib, cyclophosphamide, thalidomide, dexamethasone) reported a PFS significantly shorter in patients with del(13) by FISH compared with those with normal karyotypes[66] (Fig. 6 and Fig. 7). In a small Canadian study[65], bortezomib seems to be effective in patients with t(4;14) abnormality, while results from studies using LD combination are conflicting[47,56]. Neither bortezomib- or lenalidomide-based combination proved to overcome poor prognosis associated with 17p deletion[36,56,65]. However, no definitive conclusion can be drawn from these small retrospective trials. Moreover, other prognostic factors could be somewhat more relevant than cytogenetics in advanced disease.

An overview of new drugs of second generation

Recent early phase I and II clinical trials using new proteasome inhibitors, third-generation IMiDs and alkylating agents have produced encouraging results in terms of both efficacy and toxicity.

Novel proteasome inhibitors, such as carfilzomib (CFZ; PR-171)[67] salinosporamide (NPI-0052)[68] and CEP18770[69], will soon become part of clinical therapy. Preliminary clinical data on CFZ have been reported, while less information is available on NPI-0052 or CEP18770. CFZ is a new proteasome inhibitor that binds its target selectively and irreversibly[67,70]. Preclinical studies showed that CFZ was more potent in its ability to induce caspase-8 and caspase-9 than BTZ and could overcome bortezomib-resistance in cell lines and primary plasma cell models[67]. After phase I studies targeting B-cell-derived malignancies [71,72], several phase I/II studies investigated

the role of CFZ in patients with rrMM. In PX-171-003 study, 266 patients received CFZ 20 mg/m^2 on days 1, 2, 8, 9, 15, 16 of a 28-day cycle and, after first cycle, CFZ dose was escalated to 27 mg/m^2. Patients had received a median of 5 prior lines of therapy (range 1-20) including bortezomib (99.6%), thalidomide (74%), lenalidomide (94%) and stem cell transplantation (65%). Sixty-five percent of patients were refractory to bortezomib. At least PR was reported in 24% of patients, with a median duration of response of 7.4 months. Main grade 3-4 side effects were thrombocytopenia (22%), anemia (20%) and pneumonia (8%) whereas severe peripheral neuropathy was documented in less than 1% of patients [73]. A recent safety analysis evaluating pooled data from more than 600 patients enrolled in 4 trials confirmed that CFZ rarely induced ≥ grade 3 peripheral neuropathy [74] and, due to excellent tolerability it can be administered for prolonged periods [75]. Recent studies have reported encouraging preliminary safety and efficacy results with CFZ in patients with renal impairment (RI)[76,77] and with cytogenetic abnormalities [78]. A phase Ib dose-escalation study, evaluated CFZ in association with lenalidomide and low-dose of dexamethasone (CRd) in 40 heavily pre-treated rrMM patients. ORR for the 29 evaluable patients was 59% and median duration of response (DOR) has not been reached (median follow-up 5.2 months). No dose-limiting toxicities (DLTs) or deaths attributed to therapy have been observed. The most common ≥ grade 3 adverse events were hematological (thrombocytopenia [n=6], anemia [n=4], and neutropenia [n=6]), and all were reversible. No treatment-related neuropathy, or thrombotic events ≥ grade 3 were observed [79]. Based on these data, a Phase III international trial of CRd vs lenalidomide plus low-dose dexamethasone (Rd) in relapsed MM was started in 2010.

Pomalidomide (POM, CC4047) is another IMiD recently introduced[80,81]. In vitro studies showed that POM is more potent than the other IMiDs[82-84]. In a phase I study, POM was given at 4 dose levels (2, 3, 4, 5 mg) on days 1–21 of 28-day cycle, and 32 patients were included. Median number of prior regimens was 7 (range 2–18). MTD has not yet been reached. Eight of 21 (38%) patients treated with POM alone achieved a response (1 CR, 2 PR, 5 MR); mean TTP was 8.3 weeks (range

2–36). In 5 of 13 patients (38%), responses improved after dexamethasone was added (2 PR, 2 MR, 1 SD). Neutropenia and thrombocytopenia were the most common grade 3/4 toxicities, with no dose-dependent increase[85]. In the first phase II trial, 60 patients with rrMM received POM 2 mg daily orally, on days 1 through 28 of a 28-day cycle and dexamethasone 40 mg daily on days 1, 8, 15, 22 of each cycle. Thirty-eight patients achieved objective responses (63%) including 5% of CR and 28% of VGPR. Response rates achieved in lenalidomide- (40%)[86,87], thalidomide- (37%) and bortezomib-refractory patients (60%)[86] were also promising, and so was long-term response found in an extended follow-up of phase I study[88].

The alkylating agent bendamustine is structurally similar to both alkylating agents and purine analogs, and is not cross-resistant with alkylating agents and other drugs in vitro[89]. Bendamustine showed strong activity in MM patients, also in untreated patients[90,91]. Recently, a phase I study investigated the role of bendamustine in combination with lenalidomide and dexamethasone in patients with rrMM[92]. Seven out 9 valuable patients (67%) achieved a response, including 1 VGPR and 5 PRs. The MTD of bendamustine and lenalidomide has not been identified at this point. Grade 3/4 adverse events included neutropenia (2 patients), thrombocytopenia (1), anemia (1), hyperglycemia (1), and prolonged QT interval (1).

Several other agents targeting novel molecular mechanisms are in late-stage clinical testing (Table 3). Unfortunately, to date none of these trials has yet reported significant single-agent activity, since some of these agents may result in a more cytostatic than cytotoxic effect. Some of these compounds have also been used in combination with bortezomib or lenalidomide in phase Ib/II trials; however, it is difficult to identify the benefit of these agents when they are used in combination with active agents[93]. Numerous other investigational agents are being considered for early-phase clinical testing. Therapeutic options for MM will continue to increase, and this will substantially improve outcomes.

Expert opinion

To date, there is no strong evidence to guide physicians in the treatment choice for rrMM, and mainly post-hoc analyses are available. Randomized studies are awaited in this context.

First-line therapy choice plays an important role. All compliant patients should receive combination therapy followed by intensification and maintenance with the aim to obtain maximal tumor burden reduction. Valid options are currently available.

The studies described in this review suggest that depth of response is a key factor also in rrMM patients. Indeed, patients attaining a deeper response, in particular CR, have a prolonged PFS.

In patients with suboptimal response to induction, type of therapy represents another crucial point. The data presented here also suggest that in the non-transplant setting, therapy should be prolonged, if tolerated, beyond first response, with the aim of achieving deeper response. However, caution is necessary, and patients' characteristics, such as age, performance status, comorbidities, type of previous therapy, response and tolerance to previous treatments should be taken into account. In younger patients, data are controversial, and the role of prolonged treatment in patients failing to achieve the deepest and fastest response before transplantation remains an open issue. Before the introduction of novel drugs, young patients with suboptimal response to induction benefited most from early transplantation. However, in the era of new drugs, new data have questioned whether transplantation should be preformed early or if second-line treatment should be preferred to improve response before high-dose therapy.

Data reported in published studies showed that more intense treatment regimens including 3 of 4 drugs proved to be beneficial in rrMM. Of course, the toxicity profile of these regimens should be carefully considered. To decrease toxicity and eventually treatment discontinuation, replacing thalidomide by lenalidomide, and reducing bortezomib schedule from twice- to once-weekly administration seem to be effective actions.

As for the type of previous treatment, in patients who received prior treatment with thalidomide, bortezomib alone, as well as BCD, VTD, and VRD, led to negative results, while conflicting results were reported with LD. One study also suggested cross-resistance between thalidomide and

lenalidomide. Prior treatment with bortezomib appeared to negatively impact on outcome in patients receiving VRD, while it did not affect patients treated with PAD combination. Similarly to prior treatment with thalidomide, results with LD are conflicting in patients previously treated with bortezomib. Prior treatment with lenalidomide positively impacted on patients treated with VRD, but no substantial advantage was seen in patients who received thalidomide-based regimens. However, in our opinion, young and compliant patients in first or, at most, second relapse, who have not received multi-drug combination therapies, or who have shown an optimal outcome with them, should receive a combination therapy containing bortezomib, one IMiD, dexamethasone, and possibly one chemotherapeutic agent. This approach aims to obtain a CR, as well as long-term remission duration. On the contrary, younger patient non-compliant with or having a suboptimal outcome after multi-drug combination therapies, elderly patients, and those in third or subsequent relapse, should receive sequential therapy based on the type, side effects and effectiveness of prior therapies. Patient comorbidities, aggressiveness of disease and patients' preference should be considered as well, since there is no evidence to support a specific treatment choice in certain subgroups. The achievement of maximal response should always remain a main goal. Thalidomide with or without steroids may be more suitable in advanced stage of disease. If side effects and complications occur, palliative and supportive therapies to maintain quality of life are a reasonable option.

Consolidation and/or maintenance therapy seems to be of benefit both in combination or sequential therapies also in rrMM. Caution is necessary when using long-term thalidomide since a prolonged exposure to thalidomide may cause peripheral neuropathy, thus limiting the choice of subsequent therapies. On the contrary, lenalidomide seems to be the best candidate for long-term treatment given its safety profile and effectiveness.

To date, there is not sufficient evidence to base therapy choice for rrMM on cytogenetics.

Second generation new-drugs, such as pomalidomide, carfilzomib, bendamustine and histone-deacetylase inhibitors, showed promising preliminary results. They will probably enter the clinical

practice soon, thus expanding the treatment spectrum of multi-drug combinations, and eventually increasing the rescue possibility.

Ongoing and future studies will increase the treatment options available to rrMM patients and improve outcome

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